Epitomes

Important Advances in Clinical Medicine

Pathology

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The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and clinical importance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of progress in medicine, whether in their own field of special interest or another.

The epitomes included here were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under the direction of Yutaka Kikkawa, MD, and the panel.

Cervical Pathology—The Bethesda System and the 'Atypical Squamous Cells of Undetermined Significance' Controversy

THE BETHESDA SYSTEM for reporting cervicovaginal cytologic examinations was first introduced by the National Cancer Institute in 1988, and criteria for using uniform terms and consistently reporting these examinations were published by the Bethesda work group in 1994. Among the many reasons cited for creating this system was the recognition that Papanicolaou's original classification system did not reflect the current understanding of cervical carcinoma. Some laboratories continued to use the Papanicolaou classification system, although there was no consistency in how it was applied, and other laboratories used nomenclature borrowed from surgical pathology or created their own terminology. The Bethesda System, therefore, was designed to provide a uniform diagnostic terminology for reporting cervicovaginal cytologic examinations.

Among the most controversial aspects of the Bethesda System has been the new diagnostic category, "atypical squamous cells of undetermined significance" (ASCUS). Before the publication of system criteria, cytopathologists and technologists were uncertain which cells to place in the ASCUS category, and clinicians were unsure of the importance of this diagnosis and how to treat patients given the diagnosis. It has been recognized that the failure to use strict cytologic criteria to define an abnormal smear can result in enormous variation in the prevalence rate of abnormal Pap smears. Applying strict criteria for diagnosing ASCUS has been found to increase the cytologic detection of clinically important lesions from 25% to 61.3%.

The Bethesda work group recognizes that individual pathologists may use the ASCUS diagnosis differently. The newly published criteria emphasize, however, that ASCUS is not synonymous with previously used terms such as "atypia," "benign atypia," "inflammatory atypia," or "reactive atypia." These other terms referred to lesions currently classified by the system as "reactive cellular changes." An ASCUS diagnosis is meant to convey the differential diagnostic problem between a benign reaction to a stimulus versus a low-grade squamous intraepithelial lesion. It appears that some consistency in the application of ASCUS is being achieved. The College of American Pathologists' Interlaboratory Comparison Program in Cervicovaginal Cytology (PAP) survey indicates that by December 1993, 82.5% of the 903 participating laboratories limited the use of "atypia" terms to abnormalities of undetermined importance.

Acceptable rates for ASCUS diagnoses are currently being defined. Clinicians are suspicious of overdiagnosis that may obligate them to provide expensive and time-consuming follow-up evaluations. The Bethesda work group has suggested that the rate of ASCUS diagnoses should not exceed two to three times the rate of squamous intraepithelial lesion diagnoses. The College of American Pathologists' PAP program supports the target value of the ratio of the diagnosis of ASCUS to that of squamous intraepithelial lesion of 2:1 to 3:1 and has found that this ratio is more constant between laboratories than the ASCUS rates because patient groups may vary. Therefore, it has been suggested that the ratio of the ASCUS diagnosis to that of squamous intraepithelial lesion can be used for interlaboratory comparisons and as a monitor over time within laboratories or between individual cytopathologists and technologists. The Quality Assurance Committee of the California Breast and Cervical Cancer Control Program similarly has investigated this ratio to monitor participating laboratories. Their preliminary results indicate that this is a useful means of interlaboratory comparison and that the ASCUS diagnosis is used somewhat consistently.

The College of American Pathologists' 1993 PAP survey indicates that 62% of laboratories will qualify an ASCUS diagnosis as favoring a reactive or premalignant process, and 53% will give a written follow-up recommendation in ASCUS reports in most of these cases.

Interim guidelines for the follow-up of ASCUS Pap smears have recently been published. Future trends in the use of the system should include increased consistency in using the ASCUS diagnosis and a better understanding of the diagnostic problem this term is trying to communicate, so that appropriate follow-up can be instituted.

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Serum Prostate-Specific Antigen Assay—An Update

PROSTATE-SPECIFIC ANTIGEN (PSA) is synthesized in the epithelial cells of the prostate gland and is perhaps the best tumor marker discovered thus far. The tissue specificity of PSA makes it the most useful marker available for the diagnosis and management of prostate cancer. Lack of cancer specificity is its only drawback. Benign conditions, such as benign prostatic hyperplasia, prostatitis, and infarction, can also be associated with elevated serum PSA levels. Because prostate cancer is frequently associated with old age in men and is a major cause of death for men, a test capable of detecting prostate cancer before the lesion extends outside the confines of the prostate gland is in demand.

Clinical Utility

Because of its tissue specificity, the PSA assay is particularly useful for monitoring the success of surgical prostatectomy. Complete removal of the prostate should result in an undetectable PSA level; any measurable PSA after radical prostatectomy would indicate residual prostatic tissue or metastasis. In those cases, increasing PSA concentrations strongly indicate a recurrent disease. If, however, the detectable serum PSA level after radical prostatectomy is caused by incomplete resection of the gland and not persistent disease, the level should remain unchanged on extended follow-up. Because of the specificity of PSA, the ability of the assay to detect residual prostatic tissue or the recurrence of prostate cancer at an early stage cannot be replicated by other tumor markers. It should be noted that the half-life of serum PSA is about 3 to 4 days; therefore, it will take 30 days for a serum PSA at 50 μg per liter (50 ng per ml) to drop to an undetectable range after surgical therapy. Measuring the PSA level within a month after curative radical prostatectomy is not recommended. Also, serum PSA should not be measured during the course of irradiation treatment, as a transient and modest increase of PSA may occur that could be misinterpreted as disease progression.

The tissue specificity of PSA also makes the test an excellent tool for detecting recurrence after radical prostatectomy. There has been a great demand for the development of an ultrasensitive PSA test that would allow recurrence and metastasis to be detected early, thus providing a better opportunity for successful treatment. Many commercial PSA tests now available are capable of detecting serum PSA levels below 0.1 μg per liter.

In general, no tumor markers are recommended for screening. The use of serum PSA levels in combination with either digital rectal examination (DRE) or transrectal ultrasonography of the prostate as a screening tool for detecting clinically important prostate cancer has been recommended by some. Screening may not only prevent the death of about 30,000 to 40,000 active men from prostate cancer each year, but also permit treatment of organ-confined, potentially curable prostate cancer discovered in men with a life expectancy of more than ten years.

Improvements on Assay Use

The PSA test is tissue- but not cancer-specific. There is substantial overlap in serum PSA levels between men with benign prostatic hyperplasia and those with prostate cancer, especially in the range of 4 to 10 μg per liter. Therefore, there is also a need to improve the current PSA test to differentiate between the two disorders. Two interesting and noteworthy new approaches have been developed for improving the specificity and sensitivity of PSA testing: the measurement of PSA density and the determination of the rate of increase in PSA concentration.

One approach has been to divide the serum PSA concentration by the volume of the prostate gland (determined by transrectal ultrasonogram); the result is the PSA density. A mildly elevated serum PSA level associated with a small prostate gland may be indicative of cancer, whereas the same value in a patient with a large gland may be indicative only of benign hyperplasia. It was recommended that if the findings of the DRE are normal and the serum PSA level is between 4 and 10 μg per liter (by Hybritech assay), the patient should undergo transrectal ultrasonography to determine the volume of the prostate gland. The mean PSA density has been established as 0.285 for men with positive biopsy results and 0.199 for men with negative biopsy results. The merit of PSA density is to distinguish benign prostatic hyperplasia from prostate cancer for men who have serum PSA levels within the intermediate range (4 to 10 μg per liter) who have had normal findings on a DRE, but it may not detect all organ-confined prostate cancers.

Another approach to improve the specificity of the serum PSA test is to calculate the rate of change of serum PSA levels. This rate appears to be more useful than the actual serum PSA level for detecting and staging prostate cancer. For example, for serum PSA values well within